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09/988,013	11/16/2001	Shui-on Leung	329208	7681

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FAEGRE & BENSON LLP
PATENT DOCKETING
2200 WELLS FARGO CENTER
90 SOUTH SEVENTH STREET
MINNEAPOLIS, MN 55402-3901

EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/988,013	LEUNG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32,38 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27 and 33-37 are cancelled.

Claims 28-32 have been amended.

Claims 38-39 have been added.

2. Claims 28-32 and 38-39 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

The Power of Attorney and Change in Correspondence Address filed 4/7/2006 has been entered in full. Accordingly, all future correspondence will be addressed to: Faegre & Benson LLP, Patent Docketing, 2200 Wells Fargo Center, 90 South 7th Street, Minneapolis, MN 55402-3901.

Rejections Withdrawn

5. The objection to claim 31 in the recitation "any atoms within a complementarity determining regions...", is withdrawn in view of the amendments to the claim.

6. The objection to claim 28, step (e) in the recitation "variable domains of the light and heavy chain regions" is withdrawn in view of the amendments to the claim.

7. The objection to claim 33, step (a) in the recitation "amino acid sequences of variable domains" is withdrawn in view of the cancellation of the claim.

8. The rejection of claims 28-32 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "the human antibody" in claim 28 (lines 4-5 of step (b)) is withdrawn in view of the amendments to the claims.

9. The rejection of claim 32 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "introducing the vector" is withdrawn in view of the amendments to the claim.

10. The rejection of claims 28-32 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "to design a humanized variable domain" in claim 28, step (c) is withdrawn in view of the amendments to the claims.

11. The rejection of claims 32 and 37 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "A method of producing a humanized monoclonal antibody designed according to the method of claim..." is withdrawn in view of the amendments to claim 32 and the cancellation of claim 37.

12. The rejection of claims 28-32 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "and framework regions of the heavy chain have a sequence identity of at least 62.5% and framework regions of the light chain have a sequence identity of at least 69%..." in claim 28 step (b) is withdrawn in view of the amendments to claims.

13. The rejection of claims 29 and 34 under 35 U.S.C. 112, second paragraph for insufficient antecedent basis for the limitation "said framework regions" is withdrawn in view of the amendments to claim 29 and the cancellation of claim 34.

14. The rejection of claims 28-37 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for introducing new matter into the claims is withdrawn in view of the amendments to the claims, the new grounds of rejection set forth below and in view of the cancellation of claims 33-37.

15. The rejection of claims 28, 32-33 and 37 under 35 U.S.C. 102(b) as being anticipated by Singer et al (The Journal of Immunology, 150(7):2844-2857, April 1, 1993) is withdrawn in view of the amendments to the claims, which now require two different human frameworks for the heavy chain, and in view of the cancellation of claim 37.

16. The rejection of claims 33-37 under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] (US Patent 5,789,554, issued 8/4/1998, IDS reference A2 filed 4/30/2002) is withdrawn in view of the cancellation of the claims.

17. The rejection of claims 33-37 under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] (Molecular immunology, 32(17-18):1413-1427, 1995, cited on PTO-892 mailed 2/20/2004) is withdrawn in view of the cancellation of the claims.

Priority

18. The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, USSN 08/820,576 with which applicant argues, does not to provide adequate support in the manner provided by the first paragraph of 35 U.S.C. 112 for the present claims (see item no. 22 below).

Response to Arguments

19. The rejection of claims 28-32 and now applied to newly added claims 38-39 under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] (US Patent 5,789,554, issued 8/4/1998, IDS reference A2 filed 4/30/2002) is maintained.

The response filed 11/30/2006 states that the instant application claims priority to USSN 08/690,102, filed 7/31/96, which resulted in the Leung et al patent 5,789,554. This has been fully considered but is not found persuasive. Applicant has not been granted benefit of the earlier filing date of USSN 08/690,102, filed 7/31/96 for the following reasons. This application repeats a substantial portion of prior Application No. 08/690,102, filed 7/31/96, and adds and claims additional disclosure not presented in the prior application and thus, is a continuation-in-part (CIP) of the prior application. See the amendments to the specification filed 6/30/2005, which indicates that the instant application is a CIP of the prior applications for which benefit is sought. Should applicant desire to obtain the benefit of the filing date of the prior application, applicants' attention is directed to 35 U.S.C. 120 and 37 CFR 1.78. Applicant is reminded that a newly executed oath or declaration must be filed in any continuation-in-part application,

which application may name all, more, or fewer than all of the inventors named in the prior application. See MPEP 602.05(a).

Applicant also argues that the previous office Action asserts that each element of the claimed invention is disclosed in Leung et al, then the instant application is clearly entitled to at least the priority date of USSN 08/960,102, which resulted in the Leung et al '554 patent. This has been fully considered but is not found persuasive. Applicant appears to be confusing the issue of a species readable upon the claimed genus under 35 U.S.C 102(b) and compliance with 35 U.S.C. 112, first paragraph. In the instant case the claims are drawn to designing and making a subgenus of humanized antibodies, however, as set forth in the rejection in the previous Office Action Leung et al [a] teach a species falling within the claimed subgenus sufficient to anticipate the subgenus, however, the disclosure of a species in Leung et al is insufficient to describe the presently claimed subgenus. Thus, the disclosure of Leung et al in which the light chain LL2 CDRs were grafted onto human REI frameworks and where the heavy chain LL2 CDRs were grafted onto the human EU frameworks with the exception that human NEWM was used in place of the human EU FR4, while anticipatory of the claimed subgenus, does not provide adequate written support for the broader claimed subgenus. A subgenus is not necessarily described by a genus encompassing it and a species upon which it reads. *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). See MPEP 2131.02.

For these reasons the rejection of claims 28-32 and 38-39 under 35 U.S.C. 102(b) as being anticipated by Leung et al [a] is maintained.

20. The rejection of claims 28-32 and now applied to newly added claims 38-39 under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] (Molecular immunology, 32(17-18):1413-1427, 1995, cited on PTO-892 mailed 2/20/2004) is maintained.

Applicant argues as above against Leung et al [a] and the examiners' remarks above apply here as well and as such the rejection of claims 28-32 and 38-39 under 35 U.S.C. 102(b) as being anticipated by Leung et al [b] is maintained.

New Grounds of Objections/Rejections

Oath/Declaration

21. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: A newly executed oath or declaration must be filed in any continuation-in-part application (see amendment to the specification filed 6/30/05), which application may name all, more, or fewer than all of the inventors named in the prior application. See 37 CFR 1.63(d).

22. Claims 28-32 and 38-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

As presently amended the claims are drawn to a method of designing a amino acid sequences of variable domains of a humanized monoclonal antibody comprising comparing the amino acid sequences of the light chain and heavy chain variable domains of a monoclonal antibody to be humanized with the light and heavy chain variable domains of human antibodies, selecting frameworks from a first human antibody for the light chain and from a second and third human antibodies for the heavy

chain wherein the heavy chain FR1, FR2 and FR3 are selected from the second human antibody and FR4 is selected from the third human antibody and incorporating the framework sequences with the corresponding light an heavy chain CDRs of the monoclonal antibody to be humanized to design humanized light and heavy chain variable domain amino acid sequences, wherein FR4 is selected from the human NEWM antibody, or wherein the light chain framework regions are selected from the human REI antibody, or the heavy chain FR1, FR2 and FR3 are selected from the human EU antibody as well as a method for producing the designed humanized antibody in host cells. Thus, the claims are drawn to a method of designing and producing a subgenus of humanized antibodies that comprise just any CDRs, or comprising the heavy chain FR4 sequence of the human NEWM antibody, or comprising the light chain frameworks of human REI, or comprising the heavy chain FR1, FR2 and FR3 from the human EU antibody. The specification as filed only discloses a single monoclonal antibody LL2, which was humanized according to the claimed method in which the LL2 CDRs of the light chain were grafted onto human REI frameworks and the heavy chain CDRs were grafted onto the human EU frameworks, except for FR4, which was from the human NEWM antibody. Applicant's reliance on a single disclosed species is insufficient to support the broader scope of the claims encompassing multiple subgenus's because there is insufficient disclosure of a "representative number of species" and there is substantial variation within the subgenus's claimed. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what does not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004) ("[A] patentee of a

biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). For example, according to Gorman et al the largest unknown variable when reshaping an antibody is the selection of the human immunoglobulin variable region from which the framework sequences are derived because the framework regions hold the CDRs in their correct spatial orientation and can sometimes even participate in antigen binding. At present, there are insufficient published reshaping results to generalize a "best framework" selection strategy (Gorman et al. Proc. Natl. Acad. Sci, USA, 88:4181-4185, May 1991, particularly pg. 4182, 2nd col.). There is no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other CDRs other than the LL2 are suitable for grafting onto the human REI light chain frameworks and onto the human EU and NEWM heavy chain frameworks. Further, in contrast to the scope of the claims, Applicant's disclose that the human frameworks are selected based on the highest degree of sequence homology to the murine variable region sequences. While there may be a general method of selecting the most homologous frameworks for humanizing a given monoclonal antibody, applicants' priority documents only provide adequate written support for the humanization of murine monoclonal antibody LL2 wherein the light chain frameworks are from the human REI antibody and the heavy chain frameworks for FR1-FR3 are from the human EU antibody and heavy chain FR4 is from the human NEWM antibody. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. One of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the multiple subgenus's of the claimed method in view of the single disclosed species.

Therefore, the instant claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the instant claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the instant claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Patent Examiner
Art Unit 1643

DB
February 13, 2007